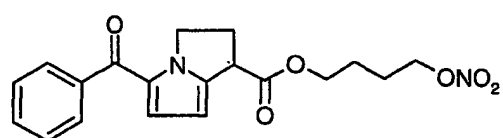
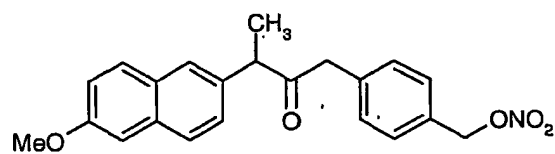


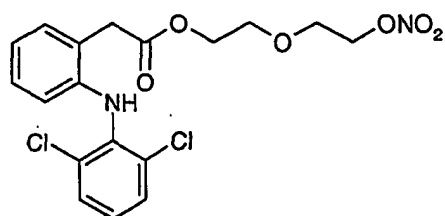
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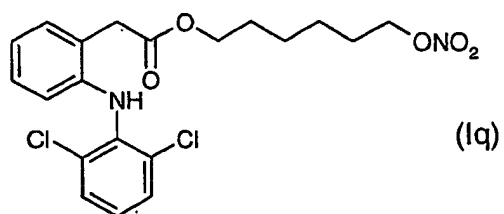
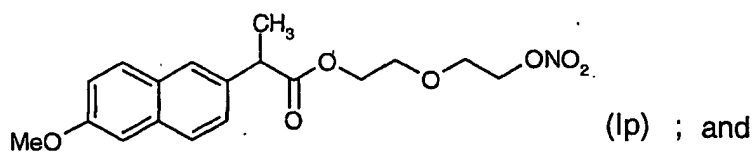
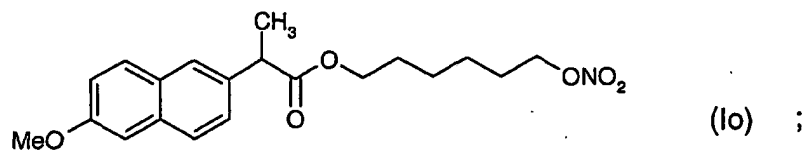
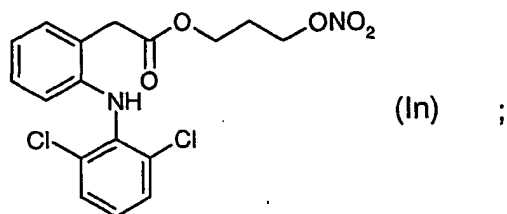
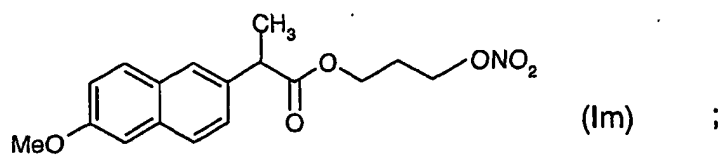
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(lk) ;

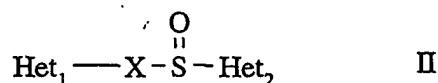


(IL) ;



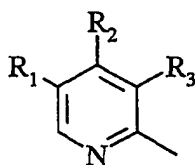
8. A pharmaceutical composition according to any one of claims 1-7, further comprising individually enteric coating layered units of an acid susceptible proton pump inhibitor, or a pharmaceutically acceptable alkaline salt thereof.

9. A pharmaceutical composition according to claim 8, wherein the acid susceptible proton pump inhibitor is selected from a compound of the general formula II or a pharmaceutically acceptable alkaline salt thereof, or one of its single enantiomer or an alkaline salt of the single enantiomer

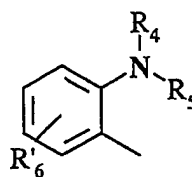


wherein

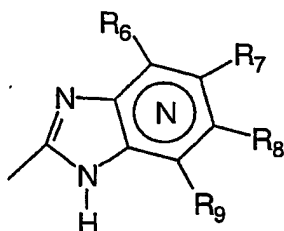
- 10 Het₁ is



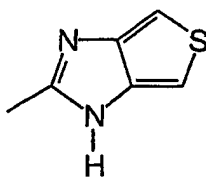
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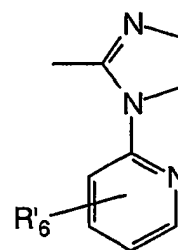
Het₂ is



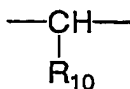
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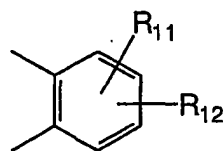
or



- 15 X =



or



wherein

- N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R_1 , R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

5 R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

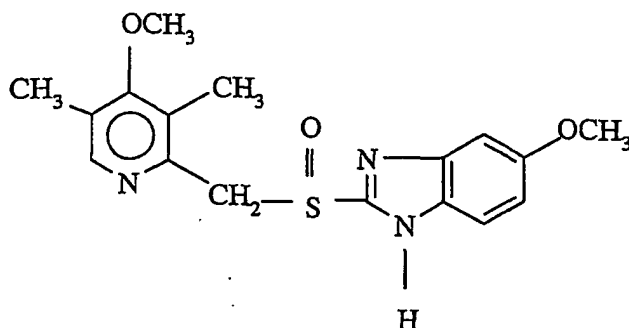
R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

10 R_6 - R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6 - R_9 form ring structures which may be further substituted;

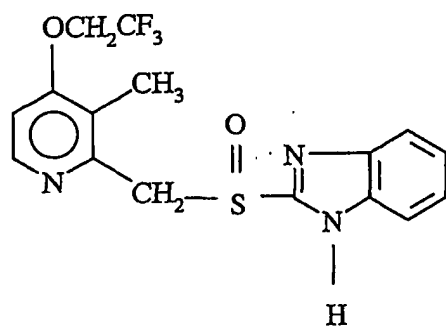
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

15 R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl; alkyl groups, alkoxy groups and moieties thereof, they may be branched or straight C_1 - C_9 -chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

20 10. A pharmaceutical composition according to claim 9, wherein the acid susceptible proton pump inhibitor is selected from the group consisting of

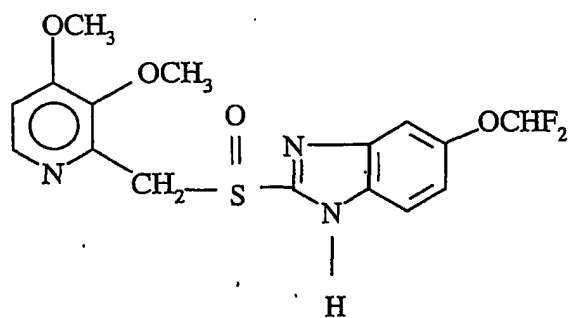


Omeprazole

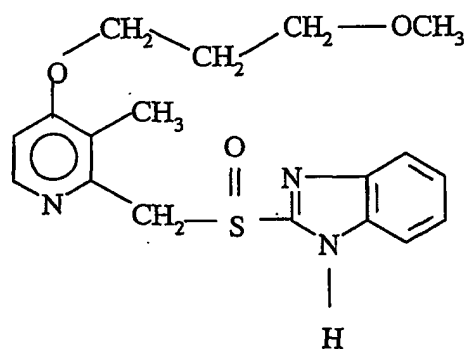


Lansoprazole

5

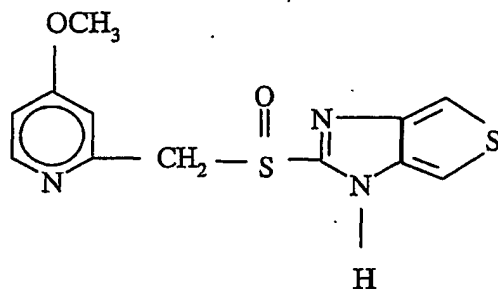
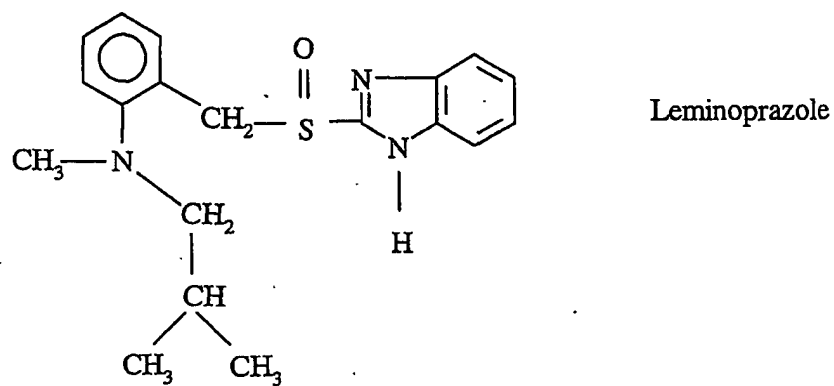


Pantoprazole

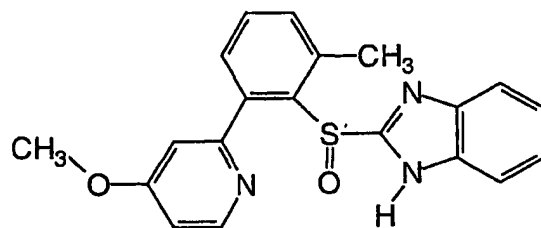
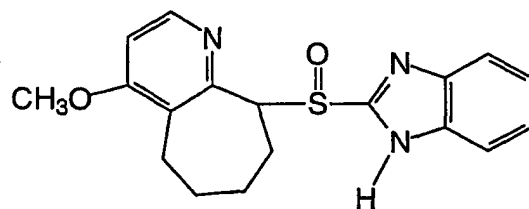


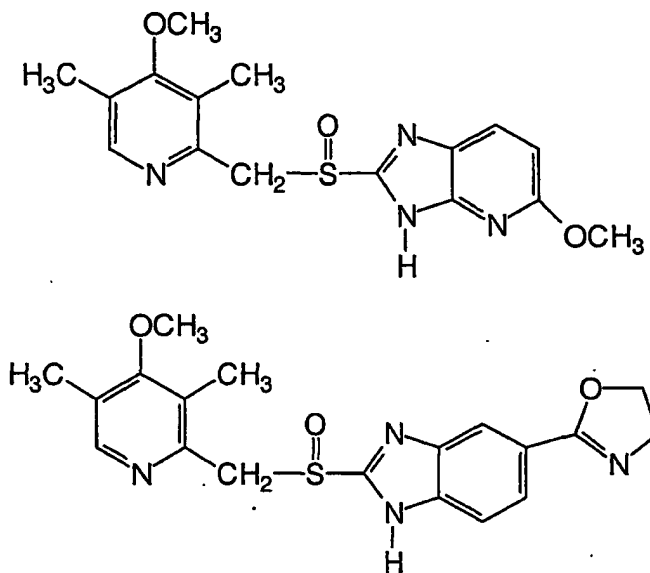
Pariprazole

10



5





11. A pharmaceutical composition according to claim 10, wherein the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt of omeprazole,
 5 (S)-omeprazole and an alkaline salt of (S)-omeprazole.
12. A pharmaceutical composition according to claim 11, wherein the alkaline salt of omeprazole or (S)-omeprazole is a magnesium salt.
- 10 13. A pharmaceutical composition according to claim 8, wherein the NO-releasing NSAID is a compound of formula Ia and the acid susceptible proton pump inhibitor is selected from the group consisting of omeprazole, an alkaline salt of omeprazole, (S)-omeprazole and an alkaline salt of (S)-omeprazole.
- 15 14. A pharmaceutical composition according to any one of claims 1-13, wherein the amount of the NO-releasing NSAID is from 50-1500 mg per unit dose.
15. A pharmaceutical composition according to claim 14, wherein the amount of the NO-releasing NSAID is from 125-500 mg per unit dose.

16. A pharmaceutical composition according to any of claims 1-15, wherein the phospholipid is lecithin.
17. A pharmaceutical composition according to claim 16, wherein the lecithin comes from
5 egg and soya, or a mixture thereof.
18. A pharmaceutical composition according to any one of claims 1-17, wherein the surfactant is a non-ionic surfactant.
19. A pharmaceutical composition according to any one of claims 1-18, wherein the non-
10 ionic surfactant is a block co-polymer.
20. A pharmaceutical composition according to claim 19, wherein the non-ionic surfactant is a poloxamer.
21. A pharmaceutical composition according to claim 20, wherein the surfactant is
15 selected from any one of Poloxamer 407; Poloxamer 401; Poloxamer 237; Poloxamer 338; Poloxamer 331; Poloxamer 231; Poloxamine 908; Poloxamine 1307; Poloxamine 1107; and polyoxyethylene polyoxybutylene block copolymer.
22. A pharmaceutical composition according to any one of claims 1-21, wherein the total
20 amount of phospholipid together with surfactant(s) is from 12.5-6000 mg per dosage form.
23. A pharmaceutical composition according to claim 22, wherein the total amount of
25 phospholipid and surfactant(s) is from 100-500 mg per dosage form.
24. A pharmaceutical composition according to any one of claims 1-23, wherein the ratio NO-releasing NSAID: phospholipid and the optional surfactant is within the range of from 1:0.1 – 1:10.

25. A pharmaceutical composition according to claim 24 wherein the ratio
NO-releasing NSAID: phospholipid and the optional surfactant is within the range of from
1:0.3 –1:3.

5 26. A pharmaceutical composition according to claim 3, wherein the oil is a vegetable oil.

27. A pharmaceutical composition according to claim 26, wherein the vegetable oil is
selected from coconut oil, corn oil, soybean oil, rape seed oil, safflower oil and castor oil.

10 28. A pharmaceutical composition according to claim 26, wherein the oil is an animalic
oil.

29. A pharmaceutical composition according to claim 28, wherein the animalic oil is a fish
oil or one or more mono-, di- or triglycerides.

15 30. A pharmaceutical composition according to claim 3, wherein the semisolid fat is
selected from mono-, di- and triglycerides.

31. A pharmaceutical composition according to claim 30, wherein the mono-, di- and
20 triglycerides are selected from the group consisting of glyceryl palmitostearate, a mixture
of mono-, di- and tri-esters of glycerol, mono- and di-esters of polyethylene glycol and free
polyethylene glycol.

32. A pharmaceutical composition according to any one of claims 4-31, wherein the
25 short-chain alcohol is selected from ethanol, propyleneglycol or glycerol.

33. A pharmaceutical composition according to any one of claims 1-32, further
comprising a co-surfactant.

34. A unit dosage form filled with a pharmaceutical composition according to any one of claims 1-33.

35. A unit dosage form according to claim 34, selected from any one of capsules, drinking
5 ampoules, dose cushion, chewable soft pill, and chewy-base lozenges.

36. A unit dosage form according to claim 35, in form of a capsule.

37. A unit dosage form according to claim 36, wherein said capsule is a hard gelatine
10 capsule.

38. A unit dosage form according to claim 36, wherein said capsule is a soft gelatine capsule.

15 39. An oral solution comprising a pharmaceutical composition according to any one of claims 1-33 dissolved in water.

40. A kit comprising a pharmaceutical composition according to any one of claims 1-33 in a unit dosage form, in combination with an acid susceptible proton pump inhibitor.

20

41. A kit according to claim 40, wherein the proton pump inhibitor is enteric coated.

42. A kit according to claim 41, wherein the proton pump inhibitor is enteric coated omeprazol.

25

43. A method for the treatment of pain, whereby a pharmaceutical composition according to any one of the preceding claims, is administered to a patient in need of such treatment.

30

44. A method for the treatment of inflammation, whereby a pharmaceutical composition according to any one of the preceding claims, is administered to a patient in need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01598

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/107, A61K 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0166088 A1 (ASTRAZENECA AB), 13 Sept 2001 (13.09.01) --	1-44
X	US 5929030 A (Y. K. HAMIED ET AL), 27 July 1999 (27.07.99) --	1-44
X	WO 0057885 A1 (PHARMACIA & UPJOHN COMPANY), 5 October 2000 (05.10.00) --	1-44
A	WO 0072838 A1 (ASTRAZENECA AB), 7 December 2000 (07.12.00) --	1-44

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

4 December 2002

Date of mailing of the international search report

06-12-2002

Name and mailing address of the ISA/
Swedish Patent Office
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01598

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5932243 A (GERD FRICKER ET AL), 3 August 1999 (03.08.99) --	1-44
A	EP 0984012 A2 (PFIZER PRODUCTS INC.), 8 March 2000 (08.03.00) -- -----	1-44

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/01598

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **43-44**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet*
2. ☒ Claims Nos.: **1**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet**
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

*

Claims 43-44 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1.(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

**

The expression "NO-releasing NSAID(s)" covers a large number of compounds with different properties and industrial applicability for all of the claimed invention has not been demonstrated. Hence the search has been restricted to compositions comprising the compounds defined in claim 5.

INTERNATIONAL SEARCH REPORT
Information on patent family members

28/10/02

International application No.

PCT/SE 02/01598

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	0166088	A1	13/09/01	AU	3787601 A	17/09/01
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				EP	1186053 A	13/03/02
				SE	0000773 D	00/00/00

US	5929030	A	27/07/99	AU	706995 B	01/07/99
				AU	6216296 A	06/03/97
				EP	0760237 A	05/03/97

WO	0057885	A1	05/10/00	AU	3883700 A	16/10/00
				EP	1165091 A	02/01/02

WO	0072838	A1	07/12/00	AU	1591500 A	29/05/00
				AU	5262300 A	18/12/00
				BG	106158 A	28/06/02
				BR	0011116 A	19/02/02
				CN	1354658 T	19/06/02
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				NO	20015855 A	30/01/02
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				SE	9904704 D	00/00/00

US	5932243	A	03/08/99	AT	106594 A	15/05/01
				AT	172297 A	15/10/01
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				BE	1008329 A	02/04/96
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				HK	1022258 A	00/00/00

Information on patent family members

PCT/SE 02/01598

28/10/02

Form PCT/ISA/210 (patent family annex) (July 1998)

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 656 881 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
14.10.1998 Bulletin 1998/42

(21) Application number: **93916129.5**

(22) Date of filing: **26.07.1993**

(51) Int Cl.⁶: **C07C 203/04, C07C 203/06,
C07D 493/04, A61K 31/62,
A61K 31/625, A61K 31/60
// (A61K31/60, 31:21),
(A61K31/60, 31:34)**

(86) International application number:
PCT/IE93/00040

(87) International publication number:
WO 94/03421 (17.02.1994 Gazette 1994/05)

(54) ESTER AND COMBINATIONS OF AN ORGANIC NITRATE AND A SALICYLATE

ESTER UND KOMBINATIONEN VON EINEM ORGANISCHEN NITRAT UND EINEM SALICYCLAT
ESTERS ET COMBINAISONS D'UN NITRATE ORGANIQUE ET D'UN SALICYLATE

(84) Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL
PT SE**

(30) Priority: **30.07.1992 IE 922474**

(43) Date of publication of application:
14.06.1995 Bulletin 1995/24

(60) Divisional application: **95201369.6 / 0 676 204**

(73) Proprietor: **CAL INTERNATIONAL LIMITED
Dublin 14 (IE)**

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Blackrock, Co Dublin (IE)**

(56) References cited:
**EP-A- 0 449 426 WO-A-92/01668
WO-A-92/16506**

- EUR. HEART J. vol. 12 SUP.A , 1991 pages 2 - 4 C.R. CONTI 'Why use a nitrate in 1990?'
- EUR. HEART J. vol. 9 SUP. A , 1988 pages 45 - 49 R. DE CATERINA 'Mechanisms for the in vivo antiplatelet effects of Isosorbide dinitrate.'
- EUR. J. CLIN. PHARMACOL. vol. 25 , 1983 pages 779 - 782 E. REY 'Pharmacological interaction between nitroglycerin and aspirin after acute and chronic aspirin treatment of healthy subjects.'
- J. CARDIOVASC. PHARMACOL. vol. 5, no. 5 , 1983 pages 874 - 877 S. WEBER 'Influence of aspirin on the hemodynamic effects of sublingual nitroglycerin.'

Remarks:

- Divisional application 95201369.6 filed on 26/07/93.
- The file contains technical information submitted after the application was filed and not included in this specification

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 0 656 881 B1

Description

The invention relates to pharmaceutical products.

The term "organic nitrates" as used in this specification refers to pharmacologically active organic nitrate compounds which relieve, or act as prophylactic against, angina pectoris.

Organic nitrates are dilators of arterial and venous smooth muscle. The dilation action on the venous system increases the venous capacity allowing pooling of venous blood. This in turn reduces the volume of blood returning to the heart thereby lessening the strains on the heart muscle by reducing the pressure in the heart chambers (ventricles). This, in turn, reduces the oxygen requirements of the heart muscle. The dilation action on the arterial system is achieved by increasing the volume of the arterial system with consequent lower resistance to blood flow. This, in turn, reduces the work that the heart is required to do. In the coronary arteries (heart) a transient widening of the arteries (vasodilation) increases blood circulation to the heart muscle thereby increasing oxygen availability to the heart muscle.

Patients with coronary artery narrowing may suffer from angina pectoris which is usually brought on by exercise, emotion or eating. The organic nitrates by virtue of their action described above relieve the symptoms of angina pectoris.

In more detail, organic nitrates act in two ways - indirectly and directly.

Indirectly: they are smooth muscle relaxants and thus dilate both arterial and venous blood vessels. At lower doses their action is mainly on the venous system resulting in a decreased right and left ventricular filling pressure. At lower doses, however, they have little effect on the systemic (arterial) filling pressure. At higher doses, the arterial effects are more marked and decreased systemic resistance is accompanied by a reduction in blood pressure (Flaherty et al 1976). The venodilating and arterial effects of nitrates relieve ischaemia (the cause of angina, pain) by reducing determinates of myocardial oxygen demand.

Directly: they relieve ischaemia by direct action on the coronary vasculature thereby increasing intercoronary collateral flow and reversal of coronary artery spasm.

One widely used organic nitrate is isosorbide mononitrate (ISMN) which is an active metabolite of Isosorbide dinitrate (ISDN). ISMN has a high bioavailability and has a comparatively long half life (4-5 hours). Thus it is very suitable for prophylactic angina therapy. This is particularly so when it is presented as a sustained release formulation.

WO-A-92/01668 describes benzoic acid substituted derivatives having cardiovascular activity.

WO-A-92/16506 describes isoindoles having cardiovascular activity.

Eur. Heart J. Vol. 12 Sup, 1991, p. 2-4 refers to the beneficial usage of nitrates.

Eur. Heart J. Vol. 9 Sup. A, 1988, p. 45-49 refers to mechanisms for in vivo anti-platelet effects of isosorbide dinitrate.

Eur. J. Clin. Pharm. Vol. 25 1983, p. 779-782 refers to the pharmacological interaction between nitroglycerin and Aspirin after acute and chronic Aspirin treatment.

J. Cardiovasc. Pharm. Vol. 5, No. 5, 1983, p. 874-877 refers to the influence of Aspirin on the hemodynamic effects of sublingual nitroglycerin.

The invention provides the use of a compound consisting of a salicylate of an esterifiable organic nitrate in the preparation of a medicament for the prophylaxis or treatment of angina and to achieve an anti-platelet effect.

The term "salicylate" refers to a salicylate or derivative or complex thereof having anti-platelet activity.

Preferably, the organic nitrate is directly esterifiable. In other words, the organic nitrate has an hydroxy group which is available for esterification.

The organic nitrate may be an isosorbide nitrate such as isosorbide 2-mononitrate or, most preferably isosorbide 5-mononitrate.

Alternatively, the organic nitrate is a glyceryl nitrate such as glyceryl trinitrate (also known as 1,2,3-Propanetriol trinitrate and Nitroglycerin).

Alternatively, the organic nitrate is a pentaerythritol nitrate such as pentaerythritol trinitrate (also known as Pentritinol).

Alternatively, the organic nitrate may be indirectly esterifiable by removal of a nitrate from the nitrate compound and replacement by an hydroxy group prior to esterification.

In this case, the organic nitrate may be selected from the group consisting of Mannitol Hexanitate, Trolnitrate Phosphate, Pentaerythritol Tetranitrate, Propatyl Nitrate, Clonitrate, and Isosorbide Dinitrate.

According to the invention there are provided the salicylates of the above-mentioned nitrates and pharmaceutical compositions containing them.

In a particularly preferred embodiment of the invention the product is formed by esterification of an esterifiable organic nitrate with acetylsalicylic acid.

The product may be adapted for oral administration or percutaneous administration.

The invention also provides a tablet or capsule comprising a pharmaceutical product of the invention.

The invention further provides a transdermal patch including a pharmaceutical product of the invention.

The invention especially preferably provides the compound Isosorbide 5-mononitrate-2-aspirinate.

In another aspect the invention provides a process for preparing a pharmaceutical product of the invention which comprises esterifying an esterifiable organic nitrate with acetylsalicylic acid.

Preferably, the esterification is carried out using a coupling reagent and/or a catalyst.

The coupling agent typically is a carbodiimide such as Dicyclohexylcarbodiimide (DCC).

The catalyst may comprise a pyridine derivative or paratoluene sulphonic acid.

Preferably, the esterification is carried out in nonaqueous conditions.

Typically, the process is carried out using methylenechloride as a solvent.

Preferably the process is carried out at a temperature below 5°C, most preferably at 0°C or below.

The invention will be more clearly understood from the following description thereof given by way of example only.

EXAMPLE 1

Synthesis of acetylsalicyloxyisosorbide mononitrate

Materials:

Acetylsalicylic acid

Isosorbide mononitrate

Dicyclohexylurea (DCC)

Dimethylaminopyridine (DMAP)

Dichloromethane (dry)

Citric acid solution (20%w/v in water)

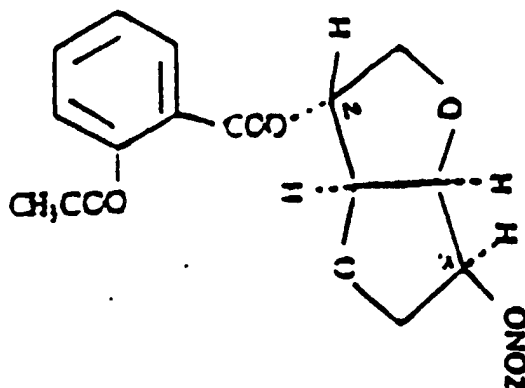
Sodium bicarbonate aqueous solution saturated

Sodium sulphate anhydrous

Method:

Add DMAP (0.03 gm) and isosorbide mononitrate (1.85gm, 0.01M) to a cold (0°C) and well stirred solution of acetylsalicylic acid (1.8gm, 0.01M) in dry dichloromethane (10ml). Gradually add DCC (2.06gm, 0.01M). Stir for 10 minutes at room temperature. Remove the precipitate by filtration. The filtered solution was washed with 2 x 25ml aliquots of cold 20% citric acid solution and then 2 x 25ml aliquots of saturated sodium bicarbonate solution. Dry the lower organic layer with anhydrous sodium sulphate filter and remove the solvent in vacuo. The product is purified on a silica column using dichloromethane as eluent. The yield of the oily semisolid product was 50-75%.

The product has the following structure:



The product may be named as Isosorbide-5-mononitrate-2-aspirinate, or 2-[2-Acetoxybenzoyl]-isosorbide-5-mononitrate, or 2-Acetylsalicyloxy-1,4:3,6-dianhydro-D-glucitol-5-nitrate.

Oil/low melting point solid

Molecular formula $C_{15}H_{15}O_9N$
Molecular weight 353

5 Infra red spectrum (thin film) 1780, 1740, 1640 cm^{-1} . The infra red analysis for isosorbide mononitrate is shown in Fig. 1. Fig. 2 is the infra red analysis for the product of the example.

Proton magnetic Resonance Spectrum See PMR BB-24 appended.

Thin Layer Chromatogram: Sigel GF 254/dichloromethane $R_f=0.8$.

10 Mass spectrum (EI) MI 353

Because of the inherent lability of the starter and product ester groupings it is necessary to select mild reaction conditions. The general method of Neises, B and Steglich, W, Angew. Chem. Int Ed Eng. 17 (1978) No. 7, 522-524 was selected because of the mild reacting condition. The direct formation of acetylsalicyloxyisosorbide-5-mononitrate from acetylsalicylic acid and isosorbide - 5-mononitrate is accomplished by the use of the coupling reagent N,N1-dicyclohexylcarbodiimide (DCC). The particular virtue of this method lies in its suitability for acid sensitive substrates such as esters. The rate of reaction is greatly increased by addition of catalytic amounts of 4-dimethylaminopyridine. Pyridine or p-toluene sulphonic acid may also be used.

20 Indirect Esterification

Acid chlorides react with primary and secondary alcohols to give esters in good yield.

Anhydrides may also be used for the esterification of alcohols in the presence of a suitable catalyst. Acidic catalysts such as sulphuric acid or zinc chloride and basic catalysts such as pyridine are generally used.

25 Direct Esterification

Direct esterification procedures involving carboxylic acids and alcohols can be accomplished by the addition of concentrated sulphuric acid or dry HCl to the reaction mixture.

30 Various methods for the preparation of esters are described in "Comprehensive Organic Transformations" - A guide to functional group preparations by Richard C. Larock, VCH Publishers Inc 1989, especially pages 966-972, 978-979, 980-981, 985-987, 989-990.

As the product of Example 1 is an oil/low melting point solid, it is likely to be particularly suitable for percutaneous application, by means of a transdermal patch or for oral application in the form of a capsule, such as a soft gelatin capsule.

A widely used organic nitrate is Isosorbide Mono or di nitrate. Such agents act directly on the coronary arteries dilating them and thus improving the blood flow to the heart muscle and thus relieving the pain of angina pectoris. Another way that organic nitrates in general relieve the pain of angina is by reducing the requirements of the myocardium (heart muscle) for oxygen by reducing the volume of blood returning to the heart.

40 The pharmaceutical products of the invention are particularly for the prophylaxis of chronic stable angina pectoris. The invention provides a new combined prophylactic therapy which will deal with the pain of angina and decrease the risk of thrombosis leading to heart attack. Patients with angina pectoris have diseased coronary arteries. All patients with this degree of diseased coronary arteries are at increased risk of developing thrombosis (or clot).

In a particularly preferred embodiment of the invention the anti-platelet agent is ASPIRIN (acetylsalicylic acid).

45 Aspirin® has been widely used for many years as an analgesic/anti-pyretic and anti-inflammatory agent. As such, it is a most useful drug. In more recent years, however, it has been discovered that aspirin has a powerful anti-platelet effect. Platelets are microscopic particles within the blood that, under certain circumstances, can stick together to form a thrombus (clot). Aspirin prevents the sticking together of platelets and thus helps prevent the occurrence of heart attack or its complications.

50 The composition may be arranged for any desired release profile. The components may be released simultaneously or in some cases the organic nitrate is released more slowly than the Aspirin.

The effect of the pharmaceutical product of the invention is in the treatment of angina pectoris and in reducing the risk of developing myocardial infarction.

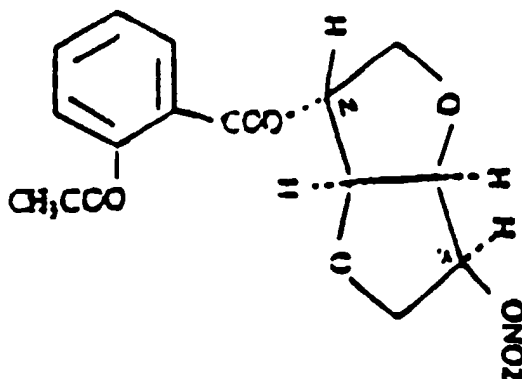
It is anticipated that, while the invention has been specifically described with reference to the combination of Isosorbide nitrate and Aspirin, it is expected that combination products of other known anti-angina agents are anti-platelet agents may also be used in combination.

Providing a nitrate and an anti platelet agent in a single dose pharmaceutical product has considerable advantages from a compliance viewpoint. If a patient is required to take a nitrate and aspirin separately there is a risk that one or

other will be forgotten. It is also quicker and easier for a doctor to prescribe such a combination product.

Claims

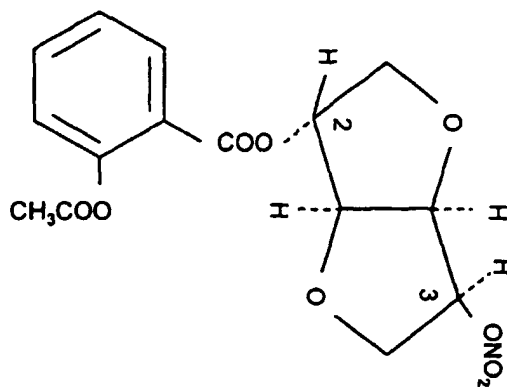
1. A salicylate ester of an organic nitrate selected from an isosorbide nitrate, a glyceryl nitrate, a pentaerythritol nitrate, mannitolhexanitate, trolnitrate phosphate, propatyl nitrate and clonitrate.
2. A salicylate ester of an organic nitrate as claimed in claim 1 selected from glyceryl trinitrate, pentaerythritol trinitrate and pentaerythritol tetranitrate.
3. A salicylate ester of an organic nitrate as claimed in claim 1 selected from isosorbide-2-mononitrate and isosorbide-5-mononitrate.
4. A compound as claimed in any of claims 1 to 3 formed by esterification of an esterifiable organic nitrate with acetylsalicylic acid.
5. A pharmaceutical composition, containing as the active ingredient a salicylate ester according to any of claims 1 to 4.
6. A pharmaceutical composition as claimed in claim 5 which is adapted for oral administration.
7. A pharmaceutical composition as claimed in claim 6 in the form of a tablet or capsule.
8. A pharmaceutical composition as claimed in claim 5 which is adapted for percutaneous administration.
9. A pharmaceutical composition as claimed in claim 8 in the form of a transdermal patch.
10. A compound of the formula:



11. A transdermal patch including a compound as claimed in claim 10
12. A soft capsule including a compound as claimed in claim 10.
13. The use of a compound consisting of a salicylate of an esterifiable organic nitrate according to claim 1 in the preparation of a medicament for the prophylaxis or treatment of angina and to achieve an anti-platelet effect.
14. The use as claimed in claim 13 wherein the esterifiable organic nitrate is indirectly esterifiable.
15. The use as claimed in claim 13 wherein the esterifiable organic nitrate is directly esterifiable.
16. The use as claimed in any of claims 13 to 15 wherein the organic nitrate comprises a compound according to any of claims 1 to 4 or 10.

Patentansprüche

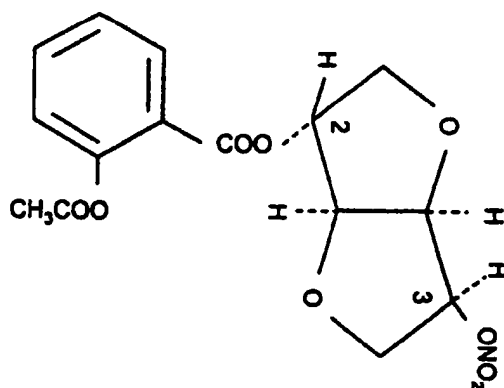
1. Salicylsäureester eines organischen Nitrates, das aus folgendem ausgewählt wird: Einem Isosorbidnitrat, einem Glycerolnitrat, einem Pentaerythritnitrat, Mannitolhexanitrat, Trolnitratphosphat, Propatylnitrat und Clonitrat.
2. Salicylsäureester eines organischen Nitrates nach Anspruch 1, das aus folgendem ausgewählt wird: Glyceroltrinitrat, Pentaerythrittrinitrat und Pentaerythrittetranitrat.
3. Salicylsäureester eines organischen Nitrates nach Anspruch 1, das aus folgendem ausgewählt wird: Isosorbid-2-mononitrat und Isosorbid-5-mononitrat.
4. Verbindung nach einem der Ansprüche 1 bis 3, die durch Veresterung eines veresterbaren organischen Nitrates mit Acetylsalicylsäure gebildet wird.
5. Pharmazeutische Zusammensetzung, die als den aktiven Bestandteil einen Salicylsäureester nach einem der Ansprüche 1 bis 4 enthält.
6. Pharmazeutische Zusammensetzung nach Anspruch 5, die zur oralen Verabreichung angepaßt wird.
7. Pharmazeutische Zusammensetzung nach Anspruch 6 in der Form einer Tablette oder Kapsel.
8. Pharmazeutische Zusammensetzung nach Anspruch 5, die zur perkutanen Verabreichung angepaßt wird.
9. Pharmazeutische Zusammensetzung nach Anspruch 8 in der Form eines Transdermalpflasters.
10. Verbindung der Formel:



11. Transdermalpflaster, einschließlich einer Verbindung nach Anspruch 10.
12. Weichkapsel, einschließlich einer Verbindung nach Anspruch 10.
13. Verwendung einer Verbindung, die aus einem Salicylat eines veresterbaren organischen Nitrates nach Anspruch 1 bei der Herstellung eines Medikamentes für die Prophylaxe oder Behandlung von Angina und zur Erlangung einer Antithrombozytenwirkung besteht.
14. Verwendung nach Anspruch 13, worin das veresterbare organische Nitrat indirekt veresterbar ist.
15. Verwendung nach Anspruch 13, worin das veresterbare organische Nitrat direkt veresterbar ist.
16. Verwendung nach einem der Ansprüche 13 bis 15, worin das organische Nitrat eine Verbindung nach einem der Ansprüche 1 bis 4 oder 10 umfaßt.

Revendication

1. Ester salicylate d'un nitrate organique choisi parmi un nitrate d'isosorbide, un nitrate de glycéryle, un nitrate de pentaérythritol, le mannitolhexanitrat, le phosphate de trolnitrate, le nitrate de propatyle et le clonitrate.
2. Ester salicylate d'un nitrate organique selon la revendication 1, choisi parmi le trinitrate de glycéryle, le trinitrate de pentaérythritol et le tétranitrate de pentaérythritol.
3. Ester salicylate d'un nitrate organique selon la revendication 1, choisi parmi l'isosorbide-2-mononitrate et l'isosorbide-5-mononitrate.
4. Composé selon l'une quelconque des revendications 1 à 3, formé par estérification d'un nitrate organique estérifiable avec de l'acide acétylsalicylique.
5. Composition pharmaceutique, contenant en tant que matière active un ester salicylate selon l'une quelconque des revendications 1 à 4.
6. Composition pharmaceutique selon la revendication 5, qui est adaptée pour une administration orale.
7. Composition pharmaceutique selon la revendication 6, sous la forme d'un cachet ou d'une gélule.
8. Composition pharmaceutique selon la revendication 5, qui est adaptée pour une administration percutanée.
9. Composition pharmaceutique selon la revendication 8, sous la forme d'un timbre transdermique.
10. Composé de formule :



11. Timbre transdermique comprenant un composé selon la revendication 10.
12. Gélule souple comprenant un composé selon la revendication 10.
13. Utilisation d'un composé constitué d'un salicylate d'un nitrate organique estérifiable selon la revendication 1 dans la préparation d'un médicament pour la prophylaxie ou le traitement de l'angine et pour obtenir un effet antiplaquettaire.
14. Utilisation selon la revendication 13, dans laquelle le nitrate organique estérifiable est estérifiable indirectement.
15. Utilisation selon la revendication 13, dans laquelle le nitrate organique estérifiable est estérifiable directement.
16. Utilisation selon l'une quelconque des revendications 13 à 15, dans laquelle le nitrate organique comprend un composé selon l'une quelconque des revendications 1 à 4 ou 10.